Al Rothenberg recording session with Dr. Joshua Lederberg at
The Rockefeller University in NYC, on Thursday, October 26, 2000.

JL: The "older, wiser and smarter" I get, the less sure I am that I have anything else to say about creativity.

AR: Really.

JL: I don't know what to say about it. It's elusive

AR: What I want to ask you today is about your own work. Your general comments about creativity are still very important.

JL: Maybe the one thing that may endure -- I don't remember all I have said about it -- but if I haven't, I would want to, that is, keeping the child alive as you get older and older and the sense of play.

AR: And you really are aware about it.

JL: Oh yes. Play on words, play on ideas, play on tricks -- being very careful that you don't hurt people in the process....

AR: [inaudible]

JL: Maybe, but my daughter did something when she was four years old and we hung it on the wall and it is absolutely astonishing. It's like a plaster mask that she cobbled a few things together and put on it. She could never do it today.

AR: That's another problem. Schools really wrenched creativity out of kids. That's terrible. Pause. That's interesting.

Let me just ask you this. Here's what you told her.

So this is about reverse mutation.

That was my first experiment with Francis. We published a paper about that. Then realizing that Neurospora wasn't working, we decided to turn around and say why do we want to do that. That was, so, we could provide a convergence between the chemical approach of extracting DNA and putting it into cells with genetic analysis, of being able to cross hyberdize whatever products you had of those transformations -- to show that there really were genic changes -- that you could map them and so forth.

So it occurred to me, and this is the sentence that I'm here to ask you about. Well, maybe we could turn the reasoning around and instead of trying to import DNA into Neurospora, maybe we could turn a bacteria into the equivalent of Neurospora by crossing it.

JL: Yes.

AR: OK. That you hadn't told me and I imagine you know why I'm particularly interested in that sentence because of my _____ process .

JL: Yes, but when you said you told her -- who's the 'her'?

AR: I got this from your lab.

JL: Is that my oral history. Maybe that's my article with Harriet.

AR: Pevzner.

JL: Oh, Pevzner. That's a 'him'. Lev.

AR: Oh, Lev. I'm sorry.

Oh, you know what it was. You said something on the phone about being interviewed by a high school student.

JL: Yes, that's Lev. There's some story about that being on the web. He was a student at Stuyvesant High School and he interviewed me purportedly to write a story for the Stuyvesant Spectator. So I was probably more open with him than I had been with almost anyone else.

AR: It sounds like that.

JL: Three or four years years later I find it on the Web. No permission ever requested or anything of the kind.

[laughter]

There was nothing awful about it. I've corrected a few factual errors.

AR: Well, that's on that particular site -- that has to do with Nobel Laureates.

JL: Entirely of his own construction. He had no permission from anybody to invoke their name. At one time it went a little bit beyond the pale and they were trying to finance it a little bit by selling advertizing. And I said, "You do not have my permission unless I have prior approval". The whole thing folded. So, it was a mute question.

AR: Well in any case....

JL: Yes, I'll stand by it.

AR: You did turn your reasoning around. You turned it on its head.

JL: Yes. I do that all the time.

AR: I know. You told me that. But in this particular case this is the recombinant ....

JL: It's what led me into doing recombination in bacteria. Right.

AR: So it really was your basic idea.

JL: It was an important event.

AR: So can you say it's how you turned your reasoning on its head.

JL: I can't reconstruct what actually happened that day. I can just give you the genre of something I will do all the time.

Most frequently, instead of asking how do I make something work -- I'll turn it around and say, let's suppose it did work. What would the world look like then. And sometimes it helps you figure out how you might discover it might happen.

AR: In this case, you turned the reasoning around. So you thought of exactly the opposite.

JL: It's just changing places. It's the opposite in the following sense. Let's see if I have conveyed what was actually involved.

Step 1. Avery publishes that DNA can go into bacteria and cause what seem like genetic changes. That's on February 1, 1944 that they publish that paper. It makes a big impact on me and many others.

Problem. Do bacteria have genes? Do we really know it is a genetic change? So, since I was working with Neurospora, so it is the easy continuity. Let's try Avery's experiment but do it in Neurospora. And if the inherited changes that you get by doing a transformation in Neurospora can be put through crosses and segregate in the same way that all the rest of the genetics of Neurospora work, nobody will question that you have moved genes into those cells and then, extending it just one step further, that genes really are DNA.

What you got from Avery is that something is DNA and something may be like genes. It is a much major event than it is today.

So, I tried it on Neurospora and have encountered a lot of facts getting in the way and decide to give up. It isn't going to work.

Turning it around, that maybe the other part of the contrast, we're accustomed to say that maybe bacteria don't have genes. They can't be crossed, maybe they can be crossed. And if we accomplish that, and do experiments like Avery on top of that, it would equally well satisfy the problematics of what I said was the problem with Avery's 1944 discovery. Namely, what's the background of insight of the genetics of bacteria.

AR: Maybe they can be crossed is not exactly saying, yes, they can be crossed.

JL: I never pin myself in saying I think "they can be". It's always a question.

AR: OK.

JL: I used to be pinned to the wall on that: did I really think there was life on Mars when I was putting so much time and effort with NASA on the Mars Lander experiments? And I never said whether there was life on Mars or not. If I knew the answer I wouldn't be figuring out how to verify it. The interesting thing is the question. Ditto here.

AR: This would mean, again, in terms of your turning it around that you would have the two opposite propositions in mind simultaneously. Would you not?

You would have the Avery position and the opposite.

JL: Well, I call it entertaining ambiguity. I think it is the same

thing as you have been describing and I insist on that all the time. That is a very important attribute of any scientist that they keep questions foremost in mind and not commit themselves in advance to the answer, except in so far, you have to have some belief in it or you're not going to bother to try. But not resolving things before the experimental data insisted that they be resolved.

AR: But this would be a belief that entertaining that a contradiction would be true at the same time.

JL: Yes, absolutely.

Entertaining is one thing. Admitting a conviction is another.

AR: Yes, but the idea is that both can be true at the same time.

JL: And that there's nothing more lovely than paradox.

AR: Except that paradox implies that they are true in sequence, not simultaneously.

JL: Well, I've encountered many paradoxes when it seems that the proposition and its contrary were both true. I love those situations. They are crying out to be resolved. And it's usually the case that either its logic is flawed or you have not stated the issue quite precisely. As you get to understand it better, than the paradox disappears. That's where I'm certain there is a phenomenon where there isn't just an artifactual error . There's nothing lovelier than a paradox. You have something you know that has to be correct. And it attacks the foundations of your thinking because it is not possible for "P" and "not P" to be simultaneously true. You've got to fix it somehow.

AR: Don't you think that the discovery is the fixing?

JL: Yes. When there is a contradiction there is a superficial explanation to it. You've got to get that straightened out first. When it gets past that point, well what should I say, Tom Kuhn has gone into this, It's a crisis. And there's nothing more fruitful -- deeper discovery -- than a deeper paradox.

AR: That's what I'm asking. That the paradox remains. That it's deeply true.

JL: Absolutely.

AR: I think the idea that it eventually has to resolve in some absolute sense is what I'm questioning if we call it paradox.

JL: Well, I don't know how we get on the semantics . One of the deepest of them and in a way the irresolvability has become one of the foundations of modern physics is the Hizenberg (sp?) Principle. You cannot know the position and momentous at the same time.

AR: OK, well that is fine. I wanted to make sure you meant that.

Now here, it goes back when I talked with you in '74. We were talking about the work you were doing at that time. This had something to do with the LARC meeting you were having a couple days before.

You said that the experimental procedure involves the action of a certain enzyme on DNA from a given bug and then that bacterium picks up the DNA and it goes through certain genetic changes.

It never occurred to me here that we were, without ever questioning, making certain assumptions about the behavior of the enzyme. And that if the enzyme were reversible, which was not mentioned in any of the previous work as far as I know, if the enzyme not only broke DNA but also could rejoin DNA pieces by exact reversal of its original mechanism that it might unify many of the other observations.

Now, are you saying here, before many other people did, that you had the idea of recombinant DNA?

JL: Pause..... Yes.

Well, he's coming in tonight. He's giving the Lederberg lecture tomorrow. You'll hear all about it tomorrow afternoon --- Stan Cohen.

He scooped me. Not long after that event, I bumped into him in a parking lot and he said, "I haven't spoken to you in a few months about what I have been doing". He told me that he had spliced DNA into a plasmid.

I've been working on it not very intelligently and not very effectively for four or five years.

AR: That's amazing. It's 1974....

JL: Oh, I've been scooped five times for every case where I ended up finishing first.

AR: What other times? Can you tell me?

JL: Have you heard about combinatorial chemistry.

AR: Sure, I have.

JL: I started working on that in 1958. On the protocol on how to go after it. And it was not until 1985 that I ran into anybody with the least bit of interest in it. By then, half a dozen people had started a new bandwagon.

That's probably the most egregious example.

AR: I can say that I recall you talking to me about it before. You have several references....

JL: Oh, that has pervaded my whole lifetime. One at the Darwinian level and one of my computer programs.

It's doing a very natural step to one of pharmaceutical discovery.

AR: And, by the way again, this is a formulation which you turn something into reverse. Is it not? And that's how you actually came to the idea in a somewhat different root from the ways others developed recombinant DNA. Did you not?

JL: This approach to it did not succeed. Others did discover a different enzyme for re-ligating DNA and for cutting it. Which raises an interesting issue -- if it's ever been looked at. The ordinary nucleases have not been demonstrated to rejoin DNA and it's not likely that they will just on energetic considerations.

I don't know if anybody has made a concerted effort to look for a trace of re-ligating activity in a nuclease. But it just occurred to me as you and I were talking that again I was turning on its head -- about the ligases -- did they ever cut DNA? And I bet a dollar to a donut that they do. Very few synthetic enzymes have no degradative activity. Many degradative enzymes show only traces of synthetic activity.

The energy flows downhill. What applies here. So -- we'll have to look that up.

But whether a nuclease could rescramble? They may not be able to resynthesize DNA; but if I have two pieces of DNA and apply nuclease just at the right time, there's a reaction that would be energetically neutral. In fact, there's a name for that activity but do we see -- it's called a gyrase -- or topoisomerase which would just interchange the pieces -- leave it at the same energy level as you had before. It's on a flat energy surface. But do the ordinary nucleases ever do that? I don't know if anyone has ever carefully looked . So we'll have to look at that again. I was thinking of that in '74 obviously.

AR: What actually were you working on when you had this idea?

JL: I was actually pursuing getting DNA spliced. I was thinking more about biological mechanisms. Here's where Stan had it all over me. I was going to put bits and pieces of DNA simultaneously into the cell and hope the cell would take care of ligating. I had the analogy of that. I knew cells would repair broken DNA and reconstitute intact chromosomes after x-ray damage so I felt certainly it would have to work -- there had to be a way to make it work using that mechanism. But getting the cells to cooperate -- I just didn't have neither the knack of doing nor in retrospect did I have a wisely chosen assay system to know what I had in effect. I had a very low efficiency level.

Stan had a very efficient assay and he was also doing the splicing in vitro with enzymes and he understood better than I did. It was a well deserved scoop on his part.

AR: He was working at the same time as you were on the same problem?

JL: Yes.

AR: Were there others working on the same problem?

JL: There were two or three others. We were not aware of it until it came out.

Paul Berg, another student of Kornberg's was.

There was another standing on its head and I had nothing to do

with it. And that's reverse transcriptase.

AR: Is that really standing on its head.

JL: Well, the same reaction goes in both directions. We had thought if you take the elementary form of the DNA dogma, and I have to explain to my friends, that when a scientist uses the word 'dogma', he is making a joke. He is not to be taken literally. He's really plastering it out on the wall.

Now you look at Watson and Crick and sometimes it is a little difficult to know when they're telling jokes but they were.

Anyhow the primitive dogma says that the information flows from DNA to RNA in protein. Reverse transcriptase says but sometimes it goes backwards from RNA back to protein.

AR: I asked Baltimore if he had gotten the idea by thinking oppositely. And he said no.

JL: So much the better.

AR: It seems strange. Doesn't it?

Unless the idea is whether Temin actually thought of it and .....

JL: No, they worked independently.

AR: That puzzled me.

On the other hand, he acknowledged that he thought that opposition had a great deal to do with creativity.

JL: Well, it could work in two ways. Creative people often evoke lively opposition .....

AR: That's another story.

[laughter]

JL: I think most people are bolstered more by concurrence than by opposition. Some people can take opposition and move it ahead anyhow. So I would put those statements in that order.

AR: But the things about opposites are that they are conceptually -- rather than socially. They relate to each other at the same

time that they are sharply different.

JL: You can get into some dialectical thinking here. Not to get too far away from that metaphor, I've always felt that the extreme left and the extreme right had much more in common than they did in the center. That's what kept me from being swallowed up by the Communist ideology. I was just barely young enough that it might have happened.

AR: Did you actually escape it? Or did you go through it?

JL: I thought it was possible for there to be two centers of evil in the world.

AR: Now really much on the same topic -- you said this.

Talking about conceptualizing the enzyme. This is another kind of thinking that I'm interested in.

You said that you "imagined yourself as an atom in the molecule that you're thinking about. And try to visualize all the environmental circumstances that would be impinging upon you. And what could happen to you if you were living there.

Was that the kind of thinking you did then? Is there visual imagery involved in that too?

JL: Less that what you might think from the statement.

Here's something for you to pursue in some detail. Maybe the "people of the book" are more literate and less iconic than others. It's only in the last century that we have had many Jewish painters and sculptors and maybe there is a tradition preceding that that one would have to recite.

OK, but what is the difference? Scriptural texts I can submit to formal reasoning. I can draw rigorous inference from statements that can be recast in the form of a syllogism. I can't do that with pictures.

Pictures are great for initiating an intuition about an object. And I use it in that way. But, as quickly as I can, I try to translate that into falsifiable propositions.

AR: You don't think you use it as an integrative process?

JL: Sure I do. But I don't trust it.

AR: You don't trust it.

JL: Because I can't prove anything from an image even though I can be beguiled by a superficial comparison etc. So, it gives me leads.

Well, I make a conscious effort to move from that plane of representation to a set of propositions as quickly as I am able to do so then I can put those through my logic machine.

AR: But you manipulate them in your mind.

JL: Well, to a degree.

AR: Do you turn things around and see the opposite side of it?

JL: Well, no. That's not usually what happens at a visual level. That usually happens after I've had a translation into a process . I put a process diagram as being part of a literal statement rather than a pictorial one because you can convert it into a set of sentences.

AR: So you wouldn't use the icon as part of a development.

JL: It's more as a preliminary to textual statements and there inverting the direction of a sense of a proposition -- subject and object things. Part of the combinatorial tricks.

Another very frequent device I use is abstraction. When I have a concrete example -- if I'm designing an experiment and it occurs to me that I'll use enzyme X even without thinking about it anymore, I'll stop myself in the tracks and say, Whoa, Josh, you thought about X . Is X the optimum answer. X is a member of a genre of things -- scan that entire genre before you decide if you're going to use X. And this is just routine instance all the time. Never accept your first image of what you think you're going to plug into a system.

AR: Do you possibly remember what this process led you to?

JL: That's the general view I always use to think about things. It happens ten times a day.

AR: Oh, you might have done that many times since that time.

JL: Yes.

AR: Routinely, do you put yourself in that position.

JL: Yes.

AR: How about other things in the enzyme.

JL: Well, I'll look at the bacterial colony and I'll see one or two of the rods at the edge and I try to think of myself what does it feel like to be there. Am I going to spread my wings and fly more out on the agar, am I going to pile them up on my neighbors, are they going to crush me at sometime. You know, things of that sort. That's what comes to my mind immediately.

AR: Recently.

JL: Like yesterday.

AR: What were you working on there?

JL: I'm looking at bacteria that grow very fast. And can you believe it that I have a specimen now -- I spread the plates at 0900 as single cells. By 5pm in the afternoon they are one millimeter size colonies. Maybe a hundred million cells in each colony.

AR: What are you looking at?

JL: I've been trying to figure out what is it that regulates the ultimate levels of the rate of growth.

So now I try to put myself in the cell and think of all the different synthetic processes . What happens between one cell division and the next. It only takes 14 mintues. What's going on during all that time. You get a catalogue of events all of which have to be kept in tune with one another in order for this miracle to take place.

AR: You also think theoretically. Don't you? Biology is not .....

JL: Well, as all other biologists.

AR: That's what I thought.

JL: Listen, I took math. I took logic. I took experimental physics as an undergraduate. I've prepared myself and I

try to get young people going into biology to follow a similar paradigm that they'll understand the foundations and they hardly ever do.

AR: But to go back to the visualization question. Aren't there times in developing theory that you might use a metaphorical structure/concept. You were just talking now about being in the colony....

JL: Yes.

AR: So do you create stable metaphors like that? Do you have a paradigm for working? A theoretical strucutre?

JL: Yes, I do but I do most of my hypothesis generation at a pretty literate level and I try to make it as formal as I am able to do. Even then, most logicians will complain that I'm overdoing it. Putting too much of a burden on formalism.

AR: Do you purposely avoid metaphors?

JL: I use them but then I go on from there. I can't build any very elaborate structure without going into something that is more like a set of sentences.

I'm also very much aware of the Plato shadows in the cave -- limitations of even close sensory experience. I've had enough physics to realize what a joke it is to talk about the color of electrons.

For those reasons I mistrust those metaphors. They can go so far. They are a proxy for certain mathematical formulas and that what will count eventually. Use them but don't trust them. It only goes so far. Very human constructs as a way we invent how to look at the world. Even something as dramatic as color. You know you reduce that to a set of wavelengths in the electromagnetic spectrum. It both diminishes and enlarges. It diminishes on an aesthetic level and enlarges by saying here is an electromagnetic spectrum. You can talk about frequency ranges from one hertz to gigahertz and more of a continuum of states of energy than the notion of color would give you.

AR: Would you use color metaphorically?

JL: Hardly ever. I just associate it too much with a spectrum -- with a wavelength number.

Now you know color is a great tag.

Did you know all DNA sequencing involves using four different color reagents that tag the next base that comes off and basically what you see in the raw data coming off the DNA sequencer is a string of color. And the colors get to be translated to ATGC respectively. But that is something we invented to make it easier to see it that the fundamental process does not depend on color. It depends on very different chemical dynamics.

AR: Just to go back to what we were talking about originally -- paradox -- do you think that metaphor is one way that you can deal with paradox? In other words, leave it as a metaphorical, instead of saying something is true and not true at the same time. That it is a metaphorical issue?

JL: I would say that the reason for the contradiction is that your assertions are indeed metaphors and when you get it straightened out, you'll be able to make much more precise statements and they will no longer be in contradiction as long as they are left at our level of understanding. That's the best that metaphors can do with us.

AR: Are you doing any more work on artificial intelligence?

JL: I would like to say yes. But I can't say that I have the time, energy or inspiration to carry it much further. I think you do know about the Dendral project. [Let me get you something about it].

AR: And so this is a program you are actually working on?

JL: No, but I am trying to extend it. We spent enormous effort to make Dendral work in a very narrow domain and I would like to find ways to generalize it. I've given two papers on it in the last five years. Not very satisfactory but trying to give some cues on how we might get at it.

Now when I mentioned about the electromagnetic spectrum important in that context, it is also related to what I said before about abstraction, exhausting the genus or sticking to the species. Many, many problems of designing experiments that provides a good hypothesis too, -- how do you best do something -- if you want to be sure that you have covered all the bases, scan the spectrum because each wavelength is also associated with

a mass number, with an energy level which reminds you of a whole universe of possibilities. Then you try to think of some heuristics so you really don't have to examine each wave number of 1001, 1002 and so forth. So there can be some rules by which you can actually lump it. It makes you think about the fundamentals on how you classify the sources of insight of information that you are going to apply to a particular problem. So you are getting efficient taxonomies of the resources that you have available is a very important part. So this is creative analysis and you try to import that into your computer systems as well.

She stresses heuristic search. That's fine for some of the universe we have to deal with but they have to be done heuristically. She doesn't prescribe combinatorial expansion. And I always want to make sure that I can cover every imaginable base. And then exclude things knowingly,not by inadvertence.

AR: And imaginable -- means logic.

JL: Well for me imaginable means logical -- arrival by some logical processes. I gave you one -- look at every wave number in the electromagnetic spectrum. Look at every mass number from electrons to the cosmos. Now, that's too dumb to work per se, but once you started on that path, then you say, ok, what rule am I going to use to break this up in useable chunks. I'll have to think about what the rule is. Not just what is delivered to me.

AR: Do you know Simon's work?

JL: Oh yes, we have a lot in common.

AR: Do you like his work?

JL: Yes and no. I mean yes, yes yes and then every now and then I would get irritated because he claimed more than he can actually include or being a little vague (in his AI work) on how you can go on to the next step.

AR: Well it is kind of formulation that all these things could have been worked out. It is almost a denial of the human creative factor in terms of what I have seen. In other words, _____ constant can be worked out through the Bacon program or something like that. That doesn't sound like what happened with Planck..

JL: Here's what happenend with Planck. Maybe bits and pieces of it are. I don't think we have learned a lot about the connections of what we can do on the computer and what is human intelligence. I have worked that fence for quite a long time but I think the ability to do comprehensive scanning is a part of what we call imagination. And I think above all, what people can do better than any computer program I have written or seen written is change the grain of resolution very abruptly in response to where you happen to be at in a given investigation. It just very flexibly talks about one wave number at a time or the whole electromagnetic structure in one piece and have a reasonably well founded intuition that that is the right thing to do at that stage. So I think there are heuristics that we employ from time to time that are not too different from the component heuristics of our computer programs. But I think they still don't put it together in an integrated fashion than in a way that we have learned how to do. Partly because we have a world experience that gives us some background. Computers don't go around foraging for food, looking for jobs, getting an education, interacting with each other socially, etc.

AR: Right, but I was really getting back to what I came to talk to you about today. You said to me , "well I turn things around to the opposite all the time". How would you put that into a computer program? I consider that to be a very critical part of your creative thinking. How would you make a computer do that?

[both talking at same time/not clear]

JL: Well, I don't know if I would do it randomly. I do it when I run out of steam in one direction.

AR: All right.

JL: But knowing that you are running out of steam is not as simple as it sounds.

AR: No. And I know that you have respect for the psychological factors that go into such a thing as running out of steam. How does the computer get to that? It stops when it gets discouraged?

JL: When it has learned on a thousand examples what we know about the end state of success to be able to estimate your progress to it, you may be able to get some heuristic clues to assess

how far you have gotten. Assessing progress is a very important element of any successful program.

Ours or theirs.

[laughter]

AR: another thing.... last year when you spoke to me about this archive of yours. You said that you had some very interesting findings that were going on that you wanted to show me. I think it had to do with combinatorial chemistry.

JL: Well, maybe I was going to show you my early invention.

AR: Can you tell me more about it.

JL: Let's see what I can dig out by way of a piece of paper.

AR: That would be great.

JL: Some pieces of that are being revived. There are a few paragraphs in there that have not been published in any way and they are going to be a piece of a patent application -- even after all this time. So you'll have to hold back on that a little bit.

AR: You said that you had that on your web site.

JL: There are two sites. What you have seen so far is a reasonably big tip of an iceberg made publicly available. A lot more has been scanned and will be part of the permanent archives but some of them will need review of some restrictions of time and so forth.

AR: Yes, but I meant that I could not get the interviews already there.

JL: Let's look at that.